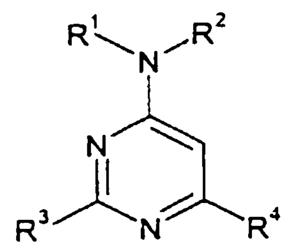
Substituted 4-amino-2-arylpyrimidines, their preparation, their use and pharmaceutical preparations comprising them

The present invention relates to compounds of the formula I,



I

in which R^1, R^2, R^3 and R^4 have the meanings indicated below, which are valuable pharmaceutical active compounds for the therapy and prophylaxis of diseases, for example of cardiovascular disorders such as high blood pressure, angina pectoris, cardiac insufficiency, thromboses or atherosclerosis. The compounds of the formula I have the ability to modulate the endogenous production of cyclic guanosine monophosphate (cGMP) and are generally suitable for the therapy and prophylaxis of disease states which are associated with a disturbed cGMP balance. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use for the therapy and prophylaxis of the designated disease states and for the production of pharmaceuticals therefor, and pharmaceutical preparations which contain compounds of the formula I.

cGMP is an important intracellular messenger, which elicits a number of pharmacological effects by means of the modulation of cGMP-dependent protein kinases, phosphodiesterases and ion channels. Examples are smooth muscle relaxation, the inhibition of platelet activation and the inhibition of smooth muscle cell proliferation and leukocyte adhesion. cGMP is produced by particulate and soluble guanylate cyclases as a response to a number of extracellular and intracellular stimuli. In the case of the particulate guanylate cyclases, the stimulation essentially takes place by means of peptide signal substances, such as the atrial natriuretic peptide or the cerebral natriuretic peptide. The soluble guanylate cyclases

(sGC), which are cytosolic, heterodimeric heme proteins, however, are essentially regulated by a family of low molecular weight, enzymatically formed factors. The most important stimulant is nitrogen monoxide (NO) or a closely related species. The importance of other factors such as carbon monoxide or the hydroxyl radical is still largely unclarified. The binding of NO to the heme with formation of a pentacoordinated heme-nitrosyl complex is discussed as an activation mechanism of activation by NO. The release associated therewith of the histidine which is bound to the iron in the basal state converts the enzyme into the activated conformation.

Active soluble guanylate cyclases are each composed of one α- and one β-subunit. Several subtypes of the subunits are described, which differ from one another with respect to sequence, tissue-specific distribution and expression in various stages of development. The subtypes α_1 and β_1 are mainly expressed in the brain and lung, while β_2 is especially found in liver and kidney. The subtype α_2 was detected in human fetal brain. The subunits designated as α_3 and β_3 were isolated from human brain and are homologous to α_1 and β_1. More recent studies point to an α_{2i} subunit, which contains an insert in the catalytic domain. All subunits show great homology in the area of the catalytic domain. The enzymes probably contain one heme per heterodimer, which is bonded via β_1-Cys-78 and/or β_1-His-105 and is part of the regulatory center.

The formation of guanylate cyclase-activating factors can be decreased under pathological conditions or increased degradation thereof can take place as a result of the increased occurrence of free radicals. The decreased activation of the sGC resulting therefrom leads, via the attenuation of the respective cGMP-mediated cell response, for example, to an increase in the blood pressure, to platelet activation or to increased cell proliferation and cell adhesion. As a result, the formation of endothelial dysfunction, atherosclerosis, high blood pressure, stable and unstable angina pectoris, thromboses, myocardial infarct, strokes or erectile dysfunction occurs. The pharmacological stimulation of the sGC offers a possibility for the normalization of cGMP production and thus allows the treatment or prevention of illnesses of this type.

For the pharmacological stimulation of sGC, until now compounds were almost exclusively used whose action is based on an intermediate release of NO, for example organic nitrates. The disadvantage of this method of treatment lies in the development of tolerance and weakening of action and the higher dose which therefore becomes necessary.

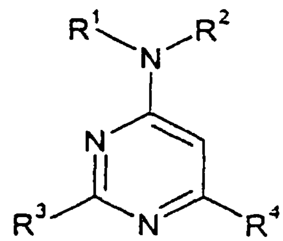
Various sGC stimulators which do not act via a release of NO were described in a series of publications by Vesely. The compounds, which are mostly hormones, plant hormones, vitamins or, for example, natural substances such as lizard toxins, however, consistently show only weak effects on cGMP formation in cell lysates (D. L. Vesely, Eur. J. Clin. Invest. 15 (1985) 258; D. L. Vesely, Biochem. Biophys. Res. Comm. 88 (1979) 1244). Stimulation of heme-free guanylate cyclase by protoporphyrin IX was detected by Ignarro et al. (Adv. Pharmacol. 26 (1994) 35). Pettibone et al. (Eur. J. Pharmacol. 116 (1985) 307) describe a hypotensive action for diphenyliodonium hexafluorophoshate and attributed this to a stimulation of sGC. Isoliquiritiginin, which shows a relaxant action on isolated rat aortas, likewise activates sGC according to Yu et al. (Brit. J. Pharmacol. 114 (1995) 1587). Ko et al. (Blood 84 (1994) 4226), Yu et al. (Biochem. J. 306 (1995) 787) and Wu et al. (Brit. J. Pharmacol. 116 (1995) 1973) detected an sGC stimulating activity of 1-benzyl-3-(5-hydroxymethyl-2-furyl)indazole and demonstrated an antiproliferative and platelet-inhibiting action. Substituted pyrazoles and condensed pyrazoles which have an sGC-stimulating action are described in EP-A-908456 and DE-A-19744027, substituted quinazolines having an action of this type in DE-A-19756388.

Various 4-amino-2-arylpyrimidines are already known. For example, in EP-A-55693 pyrimidines are described which are substituted in the 2-position by a phenyl group and which are suitable as antidotes for the protection of crop plants against the phytotoxic action of herbicides. EP-A-136976 describes 2-phenylpyrimidines which are plant growth regulators. For certain 2-phenylpyrimidines which in the 4-position can carry, inter alia, an amino group as a substituent, EP-A-555478 describes that they improve learning power and memory power.

Surprisingly, it has now been found that the pyrimidines of the formula I according to the invention bring about strong guanylate cyclase activation,

on account of which they are suitable for the therapy and prophylaxis of illnesses which are associated with a low cGMP level.

The present invention thus relates to compounds of the formula I



I

in which

R^1 is (C_1-C_8)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, R^5R^6N and aryl, (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxyl and amino, or the radical of a 5-membered to 7-membered saturated heterocyclic ring which contains one or two identical or different hetero ring members from the group consisting of O, NR^7 and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl and aryl-(C_1-C_4)-alkyl-;

and

R^2 is hydrogen, (C_1-C_8)-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkyl-$S(O)_m$-, R^5R^6N and aryl, (C_3-C_9)-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxyl and amino, or the radical of a 5-membered to 7-membered saturated heterocyclic ring which contains one or two identical or different hetero ring members from the group consisting of O, NR^7 and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl and aryl-(C_1-C_4)-alkyl-;

or

R^1R^2N is a radical, bonded via a ring nitrogen atom, of a 5-membered to 7-membered saturated heterocyclic ring which, in addition to the nitrogen atom carrying the radicals R^1 and R^2, can contain a further hetero ring member from the group consisting of O, NR^7 and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxyl, (C_1-C_4)-alkoxy, R^8R^9N, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl and R^8R^9N-CO-;

R^3 is aryl;

R^4 is (C_2-C_5)-alkyl, trifluoromethyl or aryl;

R^5 and R^6 are identical or different radicals from the group consisting of hydrogen and (C_1-C_4)-alkyl or the group R^5R^6N is a radical, bonded via a ring nitrogen atom, of a 5-membered to 7-membered saturated or unsaturated heterocyclic ring which, in addition to the nitrogen atom carrying the radicals R^5 and R^6, can additionally contain as a further hetero ring member an oxygen atom, a group $S(O)_m$ or a nitrogen atom and which can carry on ring carbon atoms one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxyl and amino and can carry on a ring nitrogen atom a radical R^7;

R^7 is hydrogen, (C_1-C_4)-alkyl, aryl-(C_1-C_4)-alkyl-, hydroxy-(C_1-C_4)-alkyl-, hydroxycarbonyl-(C_1-C_4)-alkyl-, $((C_1-C_4)$-alkoxycarbonyl)-(C_1-C_4)-alkyl-, R^8R^9N-CO-(C_1-C_4)-alkyl-, R^{10}-SO_2- or aryl, where R^7, if this group is present on a piperazino radical representing R^1R^2N, cannot be carbocyclic aryl or carbocyclic aryl-(C_1-C_4)-alkyl;

R^8 and R^9 are identical or different radicals from the group consisting of hydrogen and (C_1-C_4)-alkyl;

R^{10} is (C_1-C_4)-alkyl, aryl or R^8R^9N;

aryl is phenyl, naphthyl or heteroaryl, which can all be substituted by one or more identical or different substituents from the group consisting of halogen, (C_1-C_4)-alkyl, phenyl, CF_3, NO_2, OH, -O-(C_1-C_4)-alkyl,

-O-(C_2-C_4)-alkyl-O-(C_1-C_4)-alkyl, (C_1-C_2)-alkylenedioxy, NH_2, -NH-(C_1-C_4)-alkyl, -N((C_1-C_4)-alkyl)$_2$, -NH-CHO, -NH-CO-(C_1-C_4)-alkyl, -CN, -CO-NH_2, -CO-NH-(C_1-C_4)-alkyl, -CO-N((C_1-C_4)-alkyl)$_2$, -CO-OH, -CO-O-(C_1-C_4)-alkyl, -CHO and -CO-(C_1-C_4)-alkyl;

heteroaryl is the radical of a monocyclic 5-membered or 6-membered aromatic heterocycle or of a bicyclic 8-membered to 10-membered aromatic heterocycle, each of which contain one or more identical or different ring heteroatoms from the group consisting of N, O and S;

m is 0, 1 or 2;

in all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts,

compounds of the formula I being excluded in which, simultaneously, R^4 is tert-butyl or trifluoromethyl, R^3 is phenyl which can be substituted by one or two identical or different substituents from the group consisting of halogen, OH, -O-R^{11} and CF_3, R^1R^2N is R^{11}-NH-, (R^{11})$_2$N- or $R^{12}R^{13}N$-(CH_2)$_p$-NH-, p is 2 or 3, R^{11} is saturated unsubstituted (C_1-C_4)-alkyl and R^{12} and R^{13} are identical or different radicals from the group consisting of hydrogen and R^{11} or the group $R^{12}R^{13}N$ is a radical, bonded via a ring nitrogen atom, of a 5-membered or 6-membered saturated heterocyclic ring which, in addition to the nitrogen atom carrying the radicals R^{12} and R^{13}, can additionally contain as a further hetero ring member an oxygen atom, a sulfur atom or a nitrogen atom and which can be substituted by an aryl radical or by an aryl-(C_1-C_4)-alkyl radical, where the aryl group can be substituted by one or two identical or different substituents from the group consisting of halogen, OH, -O-R^{11} and CF_3.

If groups or substituents can occur a number of times in the compounds of the formula I, they can all independently of one another have the indicated meanings and can each be identical or different.

Alkyl radicals can be straight-chain or branched. This also applies if they are contained in other groups, for example in alkoxy groups, alkoxycarbonyl groups or in amino groups, or if they are substituted.

Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, the n-isomers of these radicals, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here is expressly also understood as meaning, in addition to saturated alkyl radicals, unsaturated alkyl radicals, i.e. alkyl radicals which contain one or more double bonds and/or one or more triple bonds, for example alkenyl radicals and alkynyl radicals. It will be appreciated that an unsaturated alkyl radical has to contain at least two carbon atoms, a (C_1-C_8)-alkyl group thus for example comprehending saturated (C_1-C_8)-alkyl radicals and unsaturated (C_2-C_8)-alkyl radicals, a (C_1-C_4)-alkyl radical comprehending saturated (C_1-C_4)-alkyl radicals and unsaturated (C_2-C_4)-alkyl radicals. Examples of unsaturated alkyl radicals are the vinyl radical, the 2-propenyl radical (allyl radical), the 2-butenyl radical, the 2-methyl-2-propenyl radical, the ethynyl radical, the 2-propynyl radical (propargyl radical) or the 3-butynyl radical. If alkyl radicals are substituted by one or more substituents, they are preferably substituted by one, two or three, in particular by one or two, identical or different substituents. Substituents can be situated on any desired carbon atoms of the alkyl radical.

Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or cyclononyl, which can all also be substituted as indicated, for example by one or more identical identical or different (C_1-C_4)-alkyl radicals, in particular by methyl, and/or by hydroxyl. If cycloalkyl radicals are substituted by one or more substituents, they are preferably substituted by one, two, three or four, in particular by one or two, identical or different substituents. Examples of such substituted cycloalkyl radicals are 4-methylcyclohexyl, 4-tert-butylcyclohexyl, 4-hydroxycyclohexyl, 4-aminocyclohexyl or 2,3-dimethylcyclopentyl. Substituents can be situated on any desired carbon atoms of the cycloalkyl radical.

Carbocyclic aryl radicals such as phenyl radicals and naphthyl radicals and heteroaryl radicals can, if not stated otherwise, be unsubstituted or carry one or more, for example one, two, three or four, identical or different substituents, which can be situated in any desired positions. If not stated otherwise, the substituents indicated in the definition of the group aryl, for example, can occur as substituents in these radicals. If nitro groups are present as substituents in compounds of the formula I, altogether only up

to two nitro groups can be present in the molecule. If an aryl radical such as, for example, a phenyl radical in turn carries a phenyl radical as a substituent, the benzene ring in the latter can also in turn be unsubstituted or substituted by one or more, for example one, two, three or four, identical or different radicals, for example by radicals from the group consisting of (C_1-C_4)-alkyl, halogen, hydroxyl, (C_1-C_4)-alkoxy, trifluoromethyl, cyano, hydroxycarbonyl, ((C_1-C_4)-alkoxy)carbonyl, aminocarbonyl, nitro, amino, (C_1-C_4)-alkylamino, di-((C_1-C_4)-alkyl)amino and ((C_1-C_4)-alkyl)carbonyl-amino.

In monosubstituted phenyl radicals, the substituent can be situated in the 2-position, the 3-position or the 4-position, in disubstituted phenyl radicals the substituents can be situated in the 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl radicals, the substituents can be situated in the 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl radicals, the substituent can be situated in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl radicals in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In polysubstituted naphthyl radicals, for example di- or trisubstituted naphthyl radicals, the substituents can also be situated in all possible positions.

If not stated otherwise, heteroaryl radicals, radicals of saturated heterocyclic rings and radicals of rings which are formed from two groups bonded to a nitrogen atom together with this nitrogen atom are preferably derived from heterocycles which contain one, two, three or four identical or different ring heteroatoms, particularly preferably from heterocycles which contain one or two or three, in particular one or two, identical or different ring heteroatoms. If not stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably, they are monocyclic or bicyclic, in particular monocyclic. The individual rings preferably contain 5, 6 or 7 ring members. Examples of monocyclic and bicyclic heterocyclic systems from which radicals occurring in the compounds of the formula I can be derived are pyrrole, furan,

thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole, 1,2-oxazole, 1,3-thiazole, 1,2-thiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxin, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridine, or phenothiazine, all in each case in saturated form (perhydro form) or in partially unsaturated form (for example dihydro form and tetrahydro form) or in maximally unsaturated form, if the forms concerned are known and stable. The heterocycles which are suitable also include, for example, the saturated heterocycles pyrrolidine, piperidine, perhydroazepine (hexamethyleneimine), piperazine, morpholine, 1,3-thiazolidine and thiomorpholine. The degree of saturation of heterocyclic groups is indicated in the individual definitions. Unsaturated heterocycles can, for example, contain one, two or three double bonds in the ring system, 5-membered rings and 6-membered rings in monocyclic and polycyclic heterocycles can, in particular, also be aromatic.

Heterocyclic radicals can be bonded via any suitable ring carbon atom. Nitrogen heterocycles, for example pyrrole, imidazole, pyrrolidine, piperidine, hexamethyleneimine, 1,3-thiazolidine, morpholine, thiomorpholine, piperazine etc., can also be bonded via any suitable ring nitrogen atom, in particular if the nitrogen heterocycle concerned is bonded to a carbon atom. For example, a thienyl radical can be present as a 2-thienyl radical or 3-thienyl radical, a furan radical as a 2-furyl radical or 3-furyl radical, a pyridyl radical as a 2-pyridyl radical, 3-pyridyl radical or 4-pyridyl radical, a piperidine radical as a 1-piperidinyl radical (= piperidino radical), 2-piperidinyl radical, 3-piperidinyl radical or 4-piperidinyl radical, a (thio)morpholine radical as a 2-(thio)morpholinyl radical, 3-(thio)morpholinyl radical or 4-(thio)morpholinyl radical (= (thio)morpholino radical). A radical which is derived from 1,3-thiazole can be bonded via the 2-position, the 3-position, the 4-position or the 5-position, a radical which is derived from imidazole can be bonded via the 1-position, the 2-position, the 4-position or the 5-position.

If not stated otherwise, the heterocyclic groups can be unsubstituted or can carry one or more, for example one, two, three or four identical or different substituents. The substituents in heterocycles can be situated in any desired positions, for example in a 2-thienyl radical or 2-furyl radical in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl radical or 3-furyl radical in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl radical in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl radical in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl radical in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. If not stated otherwise, the substituents which can occur are, for example, the substituents indicated in the definition of the group aryl, in the case of saturated or partially unsaturated heterocycles as further substituents also the oxo group and the thioxo group. Substituents on a heterocycle and also substituents on a carbocycle can also form a ring, further rings can thus be fused to a ring system such that, for example, cyclopenta-fused, cyclohexa-fused or benzo-fused rings can be present. If not stated otherwise, possible substituents on a substitutable nitrogen atom of a heterocycle are, for example, unsubstituted and substituted (C_1-C_4)-alkyl radicals, aryl radicals, acyl radicals such as -CO-(C_1-C_4)-alkyl or -CO-aryl, or sulfonyl radicals such as -SO_2-(C_1-C_4)-alkyl or -SO_2-aryl. Suitable sulfur heterocycles can also be present as S-oxides or S,S-dioxides, i.e. they can contain the group S(=O) or the group $S(=O)_2$ instead of a sulfur atom. Suitable nitrogen heterocycles can also be present as N-oxides or as quaternary salts with an anion derived from a physiologically tolerable acid as a counterion. Pyridyl radicals can be present, for example, as pyridine N-oxides.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

The present invention includes all stereoisomeric forms of the compounds of the formula I. Asymmetric centers contained in the compounds of the formula I can all independently of one another have the S configuration or the R configuration. The invention includes all possible enantiomers and

diastereomers, as well as mixtures of two or more stereoisomeric forms, for example mixtures of enantiomers and/or diastereomers, in all ratios. The invention thus relates to enantiomers in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the presence of cis/trans isomerism, for example on double bonds or cycloalkyl groups, the invention relates both to the cis form and the trans form and mixtures of these forms in all ratios. Individual stereoisomers can be prepared, if desired, by resolution of a mixture by customary methods, for example by chromatography or crystallization, by use of stereochemically homogeneous starting substances in the synthesis or by stereoselective synthesis. If appropriate, derivatization can be carried out before separation of stereoisomers. The separation of a stereoisomer mixture can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate in the course of the synthesis. If mobile hydrogen atoms are present, the present invention also includes all tautomeric forms of the compounds of the formula I.

If the compounds of the formula I contain one or more acidic or basic groups, the invention also relates to the corresponding physiologically or toxicologically tolerable salts, in particular the pharmaceutically utilizable salts. Thus the compounds of the formula I which contain acidic groups, can be present on these groups, and can be used according to the invention, for example as alkali metal salts, alkaline earth metal salts or as ammonium salts. Examples of such salts are sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines, for example ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula I which contain one or more basic, i.e. protonatable, groups can be present, and can be used according to the invention, in the form of their acid addition salts with physiologically tolerable inorganic or organic acids, for example as salts with hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid,

citric acid, adipic acid etc. If the compounds of the formula I simultaneously contain acidic and basic groups in the molecule, in addition to the salt forms outlined the invention also includes internal salts or betaines (zwitterions). Salts can be obtained from the compounds of the formula I by customary processes known to the person skilled in the art, for example by combination with an organic or inorganic acid or base in a solvent or dispersant, or alternatively from other salts by anion exchange or cation exchange. The present invention also includes all salts of the compounds of the formula I which, because of low physiological tolerability, are not directly suitable for use in pharmaceuticals, but are suitable, for example, as intermediates for chemical reactions or for the preparation of physiologically tolerable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates or adducts with alcohols, and also derivatives of the compounds of the formula I such as, for example, esters and amides, and prodrugs and active metabolites.

Preferably, R^1 is $(C_1\text{-}C_8)$-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxyl, $(C_1\text{-}C_4)$-alkoxy, $(C_1\text{-}C_4)$-alkyl-$S(O)_m$-, R^5R^6N and aryl, or $(C_3\text{-}C_9)$-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxyl and amino. Preferably, R^2 is hydrogen, $(C_1\text{-}C_8)$-alkyl which can be substituted by one or more identical or different substituents from the group consisting of hydroxyl, $(C_1\text{-}C_4)$-alkoxy, $(C_1\text{-}C_4)$-alkyl-$S(O)_m$-, R^5R^6N and aryl, or $(C_3\text{-}C_9)$-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxyl and amino. It is particularly preferred if R^1 is $(C_1\text{-}C_8)$-alkyl or $(C_3\text{-}C_9)$-cycloalkyl and R^2 is hydrogen or if R^1 and R^2 are identical or different $(C_1\text{-}C_8)$-alkyl, where all radicals can be unsubstituted or substituted as indicated. It is very particularly preferred if R^1 is $(C_3\text{-}C_9)$-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of $(C_1\text{-}C_4)$-alkyl, hydroxyl and amino, and R^2 is hydrogen. If R^1 is $(C_3\text{-}C_9)$-cycloalkyl which can be substituted by one or more identical or different substituents from the group consisting of $(C_1$-

C_4)-alkyl, hydroxyl and amino, or the radical of a 5-membered, 6-membered or 7-membered saturated heterocyclic ring which contains one or two identical or different hetero ring members from the group consisting of O, NR^7 and $S(O)_m$ and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl and aryl-(C_1-C_4)-alkyl-, then R^2 is preferably hydrogen. An alkyl radical representing R^1 or R^2 is preferably an unsubstituted or substituted (C_1-C_4)-alkyl radical. A (C_3-C_9)-cycloalkyl radical representing R^1 or R^2 is preferably an unsubstituted or substituted (C_3-C_7)-cycloalkyl radical.

In addition to the abovementioned preferred meanings of R^1 and R^2, it is furthermore preferred if the group R^1R^2N is a radical, bonded via a ring nitrogen atom, of a 5-membered, 6-membered or 7-membered saturated heterocyclic ring which, in addition to the nitrogen atom carrying the radicals R^1 and R^2, can additionally contain as a further hetero ring member an oxygen atom, a group $S(O)_m$ or a nitrogen atom carrying a radical R^7 and which can be substituted by one or more identical or different substituents from the group consisting of (C_1-C_4)-alkyl, hydroxyl, (C_1-C_4)-alkoxy, R^8R^9N, hydroxycarbonyl, (C_1-C_4)-alkoxycarbonyl and R^8R^9N-CO-. A radical representing R^1R^2N of a heterocyclic ring is preferably derived from a 5-membered or 6-membered saturated heterocyclic ring, particularly preferably from piperidine, morpholine, thiomorpholine (and its S-oxide and S,S-dioxide) or piperazine, which can all be substituted as indicated, very particularly preferably from unsubstituted piperidine, morpholine or thiomorpholine (and its S-oxide and S,S-dioxide) or from N-methylpiperazine.

The aryl group representing R^3 is preferably unsubstituted or substituted phenyl, particularly preferably substituted phenyl, very particularly preferably phenyl, which is substituted by one or two substituents from those indicated above for aryl. Especially preferably, R^3 is phenyl which is substituted by one or two identical or different substituents from the group consisting of halogen and (C_1-C_4)-alkyl, moreover preferably phenyl which is substituted by chlorine or methyl. The substituent in a monosubstituted phenyl group representing R^3 is preferably in the para-position.

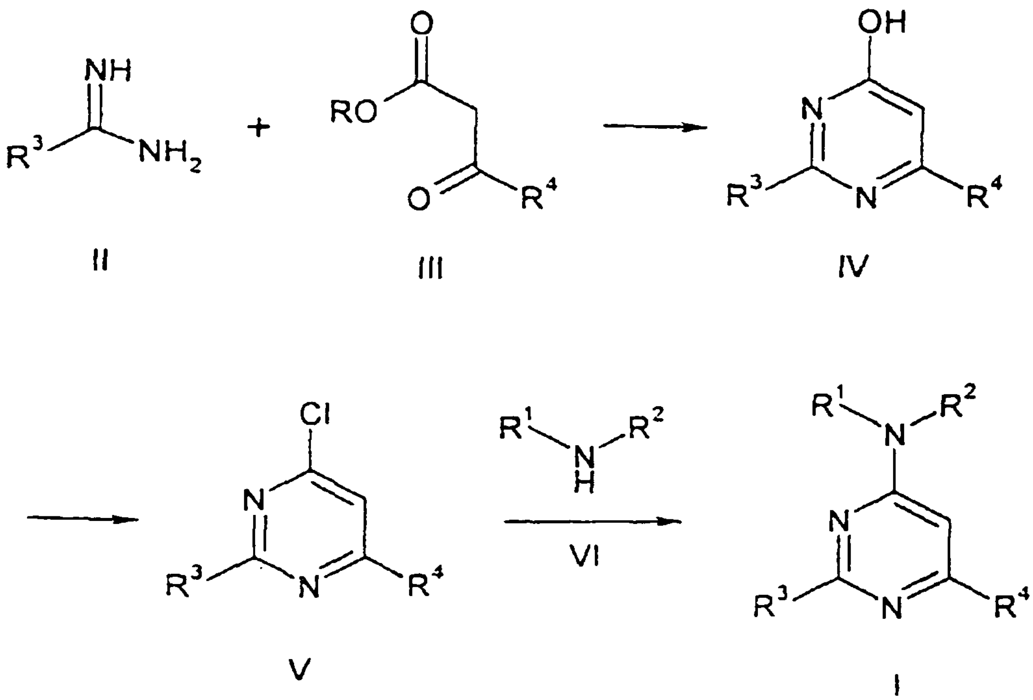
R^4 is preferably (C_2-C_5)-alkyl, trifluoromethyl or unsubstituted or substituted phenyl, particularly preferably straight-chain or branched (C_3-C_4)-alkyl, for example n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl.

Aryl is preferably phenyl or 5-membered or 6-membered monocyclic heteroaryl having one or two, in particular one, heteroatom from the group consisting of N, O and S, which can be substituted as indicated, particularly preferably unsubstituted or substituted phenyl or unsubstituted pyridyl, thienyl or furyl, very particularly preferably unsubstituted or substituted phenyl or unsubstituted pyridyl.

Preferred compounds of the formula I are those in which one or more of the radicals contained therein have preferred meanings, the present invention relating to all combinations of preferred substituent definitions. The present invention also includes, of all preferred compounds of the formula I, all their stereoisomeric forms and mixtures thereof in all ratios, and their physiologically tolerable salts.

The present invention also relates to processes for the preparation of the compounds of the formula I, which are explained below and by which the compounds according to the invention are obtainable. The compounds of the formula I can be prepared by first reacting an amidine of the formula II in an manner known per se with a 3-oxopropionic acid ester of the formula III carrying a radical R^4 in the 3-position to give a 4-hydroxypyrimidine of the formula IV. R in the formula III is, for example, (C_1-C_4)-alkyl such as methyl or ethyl. The hydroxypyrimidine of the formula IV is then activated, for example by conversion into a 4-halopyrimidine. For example, the compound of the formula IV can be converted into the 4-chloropyrimidine of the formula V by reaction with a phosphorus halide such as phosphorus oxychloride. By reaction of the compound of the formula V (or of another reactive derivative of the hydroxypyrimidine) with the desired amine of the formula VI, the compound of the formula I according to the invention is then obtained with replacement of the chlorine by the amino group. Suitable solvents for this replacement reaction are, for example, water, alcohols such as methanol, ethanol or isopropanol, ethers such as tetrahydrofuran or dioxane, amides such as dimethylformamide (DMF) or

N-methylpyrrolidone (NMP), or hydrocarbons or halogenated hydrocarbons such as benzene, toluene, xylene, chlorobenzene or dichlorobenzene.



The reactions for the synthesis of the compounds of the formula I can be carried out in a wide temperature range. Reaction temperatures of 20°C to 150°C are preferred. The reactions can be accelerated by addition of suitable bases such as, for example, sodium bicarbonate, sodium carbonate, potassium carbonate, sodium alkoxides, triethylamine or pyridine, in the first and in the last step additionally also by an excess of amidine of the formula II or amine of the formula VI. Instead of the free amidines of the formula II, the corresponding amidinium salts can also be employed. In this case, it is particularly convenient to carry out the first step with addition of bases. The intermediates of the formula IV and V and the final compounds of the formula I can be separated from the respective reaction mixture by customary processes such as crystallization, sublimation, chromatography or distillation and, if desired, purified, however, depending on the circumstances of the individual case, the intermediates can be reacted further also without intermediate isolation. Moreover, functional groups in the compounds obtained can be converted.

For example, thioether groups can be converted into sulfones or sulfoxides by oxidation with a peroxy compound such as 3-chloroperbenzoic acid or monoperoxyphthalic acid or hydrogen peroxide, or carboxylic acid ester groups can be hydrolyzed to the carboxylic acids.

All reactions for the synthesis of the compounds of the formula I are well known per se to the person skilled in the art and can be carried out under standard conditions according to or analogously to literature procedures, such as are described, for example, in Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the conditions of the individual case, it may also be advantageous or necessary for the avoidance of side reactions in the synthesis of the compounds of the formula I to temporarily block certain functional groups by the introduction of protective groups and then later to liberate them again or to employ functional groups first in the form of precursors, from which the desired functional group is then produced in a later step. Such synthesis strategies and the protective groups or precursors suitable for the individual case are known to the person skilled in the art. The starting amidines of the formula II or their salts, the oxoesters of the formula III and the amines of the formula VI are commercially obtainable or can be prepared by or analogously to known processes.

The compounds of the formula I according to the invention bring about an increase in the cGMP concentration by means of the activation of soluble guanylate cyclase (sGC) and are therefore valuable agents for the therapy and prophylaxis of illnesses which are associated with a low or reduced cGMP level or are caused by such a level or for whose therapy or prophylaxis an increase in the cGMP level present is desired. The activation of sGC by the compounds of the formula I can be investigated, for example, in the activity assay described below.

Illnesses and pathological conditions which are associated with a low cGMP level or in which an increase in the cGMP level is desired and for whose therapy and prophylaxis compounds of the formula I can be employed are, for example, cardiovascular disorders such as endothelial dysfunction, diastolic dysfunction, atherosclerosis, high blood pressure,

stable and unstable angina pectoris, thromboses, restenoses, myocardial infarcts, strokes, cardiac insufficiency or pulmonary hypertension, or, for example, erectile dysfunction, bronchial asthma, chronic renal insufficiency and diabetes. Compounds of the formula I can moreover be employed in the therapy of liver cirrhosis and for improving restricted learning capacity or memory power.

The compounds of the formula I and their physiologically tolerable salts can thus be used in animals, preferably in mammals, and in particular in humans, as pharmaceuticals on their own, in mixtures with one another or in the form of pharmaceutical preparations. The present invention therefore also relates to the compounds of the formula I and their physiologically tolerable salts for use as pharmaceuticals, their use for the normalization of a disturbed cGMP balance and in particular their use in the therapy and prophylaxis of the abovementioned syndromes, and their use for the production of medicaments therefor. The present invention furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an efficacious dose of at least one compound of the formula I and/or of a physiologically tolerable salt thereof as an active constituent and a pharmaceutically tolerable carrier, i.e. one or more customary pharmaceutically tolerable vehicles and/or excipients (or additives).

The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, film-coated tablets, coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration, however, can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of injection solutions or infusion solutions. Further possible administration forms are, for example, percutaneous or topical application, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or administration by inhalation in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the illness to be treated and its severity.

The pharmaceutical preparations normally contain 0.2 to 500 mg, preferably 1 to 200 mg, of active compound of the formula I and/or its physiologically tolerable salts; depending on the nature of the preparation and the intended use the amount of the active compound contained can also be larger. The pharmaceutical preparations can be produced in a manner known per se. For this, one or more compounds of the formula I and/or their physiologically tolerable salts are brought, together with one or more solid or liquid pharmaceutical vehicles and/or additives and, if desired, in combination with other pharmaceutical active compounds having therapeutic or prophylactic action, into a suitable administration form or dose form, which can then be used as a pharmaceutical in human or veterinary medicine. The pharmaceutical preparations normally contain 0.5 to 90 percent by weight of the compounds of the formula I and/or their physiologically tolerable salts.

For the production, for example, of pills, tablets, coated tablets and hard gelatin capsules, it is possible to use lactose, starch, for example corn starch, or starch derivatives, talc, stearic acid or its salts, etc. Vehicles for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils etc. Suitable vehicles for the preparation of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, physiological saline solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils etc. The compounds of the formula I and their physiologically tolerable salts can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations or infusion preparations. Suitable vehicles for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

In addition to the active compounds and vehicles, the pharmaceutical preparations can additionally contain customary excipients or additives, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweetening agents, colorants, flavorings, aromatizers, thickening agents, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dose of the active compound of the formula I to be administered and/or of one of its physiologically tolerable salts depends on the individual case and is to be suited to the individual conditions as customary for an optimal action. Thus it depends on the nature and severity of the illness to be treated, on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the potency and duration of action of the compounds employed, on whether the therapy is acute or chronic or prophylaxis is carried out, or on whether further active compounds are administered in addition to compounds of the formula I. In general, a daily dose of approximately 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg per kg of body weight) is appropriate in the case of administration to an adult of about 75 kg in weight to achieve the desired action. The daily dose can be administered in a single dose or, in particular in the case of administration of relatively large amounts, divided into a number of, for example two, three or four, individual doses. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

The compounds of the formula I activate the soluble guanylate cyclase. On account of this property, apart from as pharmaceutical active compounds in human medicine and veterinary medicine, they can also be used as a scientific tool or as an aid for biochemical investigations in which an effect on guanylate cyclase of this type is intended, and also for diagnostic properties, for example in the in vitro diagnosis of cell or tissue samples. In addition, the compounds of the formula I and their salts, as already mentioned above, can serve as intermediates for the preparation of further pharmaceutical active compounds.

The following examples illustrate the invention without restricting it.

Examples

Example 1

2-(4-Chlorophenyl)-4-hydroxy-6-isopropylpyrimidine

A mixture of 19.1 g of 4-chlorobenzamidine hydrochloride, 15.8 g of ethyl 4-methyl-3-oxopentanoate, 11.2 g of potassium tert-butoxide and 200 ml of

ethanol was heated under reflux for 2 hours. After cooling to room temperature, the solid was filtered off with suction, washed with water and with a little ethanol and dried at 40°C in vacuo. Yield: 12.5 g.
M.p.: 164°C.

The following were prepared analogously:

Example 2
2-(4-Chlorophenyl)-4-hydroxy-6-trifluoromethylpyrimidine; m.p.: 258°C.

Example 3
2-(4-Chlorophenyl)-6-tert-butyl-4-hydroxypyrimidine; m.p.: 193°C.

Example 4
2-(4-Chlorophenyl)-4-hydroxy-6-phenylpyrimidine; m.p.: 306°C.

Example 5
2-(4-Methylphenyl)-4-hydroxy-6-isopropylpyrimidine; m.p.: 164°C.

Example 6
2-(3,5-Dichlorophenyl)-4-hydroxy-6-isopropylpyrimidine; m.p.: 203°C.

Example 7
2-(4-Aminocarbonylphenyl)-4-hydroxy-6-isopropylpyrimidine; m.p.: 294°C.

Example 8
4-Chloro-2-(4-chlorophenyl)-6-isopropylpyrimidine
The mixture of 12 g of 2-(4-chlorophenyl)-4-hydroxy-6-isopropylpyrimidine and 35 ml of phosphorus oxychloride was heated at 90°C for 3 hours with stirring. Most of the excess of the phosphorus oxychloride was distilled off in vacuo, and the residue was added to 100 ml of ice water and stirred. The solid white precipitate forming was filtered off with suction and dried in vacuo at room temperature.
Yield: 11.4 g
M.p.: 74°C

The following were prepared analogously:

Example 9

4-Chloro-2-(4-chlorophenyl)-6-trifluoromethylpyrimidine; m.p.: 76°C

Example 10

4-Chloro-2-(4-chlorophenyl)-6-tert-butylpyrimidine; m.p.: 93°C

Example 11

4-Chloro-2-(4-chlorophenyl)-6-phenylpyrimidine; m.p.: 127°C.

Example 12

4-Chloro-2-(4-methylphenyl)-6-isopropylpyrimidine; m.p.: oil

Example 13

4-Chloro-2-(3,5-dichlorophenyl)-6-isopropylpyrimidine; m.p.: 59°C

Example 14

4-Chloro-2-(4-cyanophenyl)-6-isopropylpyrimidine of m.p. 114°C was obtained in an analogous reaction starting from 2-(4-aminocarbonylphenyl)-4-hydroxy-6-isopropylpyrimidine.

Example 15

2-(4-Chlorophenyl)-6-isopropyl-4-((2,2,6,6-tetramethylpiperidin-4-yl)amino)-pyrimidine dihydrochloride

A mixture of 534 mg of 4-chloro-2-(4-chlorophenyl)-6-isopropylpyrimidine and 1.8 g of 4-amino-2,2,6,6-tetramethylpiperidine was heated at 150°C for 2 hours with stirring. After cooling, 20 ml of water were added and the mixture was stirred at room temperature. The white precipitate was filtered off with suction, dried in vacuo and taken up in 20 ml of ethyl acetate. By addition of hydrogen chloride, the title compound was precipitated, filtered off with suction and dried in vacuo. Yield: 0.8 g.

M.p.: 359°C

Example 16

2-(4-Chlorophenyl)-6-isopropyl-4-morpholinopyrimidine

A mixture of 267 mg of 4-chloro-2-(4-chlorophenyl)-6-isopropylpyrimidine and 522 mg of morpholine was heated at 130°C for 2 hours. After cooling,

20 ml of water were added, the mixture was stirred, and the solid was filtered off with suction and dried at 50°C in vacuo. Yield: 0.28 g.
M.p.: 123°C

The following compounds of the formula I were prepared analogously to Examples 15 and 16. If an acid is specified in the column "M.p.", the compound was obtained in the form of the acid addition salt with the specified acid. The specification "2HCl" means that the compound was obtained as a dihydrochloride.

Ex. No.	R^4	R^3	R^1R^2N	M.p. (°C)
17	CF_3	4-Chlorophenyl	(3-Phenylpropyl)amino	Oil
18	CF_3	4-Chlorophenyl	(2-Ethylthioethyl)amino	114 (HCl)
19	CF_3	4-Chlorophenyl	(1-Benzylpiperidin-4-yl)amino	128 (2HCl)
20	CF_3	4-Chlorophenyl	4-(2-Hydroxyethyl)piperazino	119
21	Isopropyl	2-Pyridyl	Benzylamino	150
22	Isopropyl	2-Pyrazinyl	Thiomorpholino	107
23	Isopropyl	4-Methylphenyl	(3-Methoxypropyl)amino	Oil
24	Isopropyl	4-Methylphenyl	Cyclopentylamino	66
25	Isopropyl	4-Methylphenyl	(trans-4-Hydroxycyclo-hexyl)amino	Oil
26	Isopropyl	4-Chlorophenyl	(3-Methoxypropyl)amino	Oil
27	Isopropyl	4-Chlorophenyl	4-Methylpiperazino	292 (2HCl)
28	Isopropyl	4-Chlorophenyl	Piperidino	75
29	Isopropyl	4-Chlorophenyl	Pyrrolidino	215 (HCl)
30	Isopropyl	4-Chlorophenyl	Thiomorpholino	215 (HCl)
31	Isopropyl	4-Chlorophenyl	(2-(3-Methoxyphenyl)ethyl)-amino	213 (HCl)
32	Isopropyl	4-Chlorophenyl	Butylamino	Oil
33	Isopropyl	4-Chlorophenyl	Diethylamino	Oil

Ex. No.	R^4	R^3	R^1R^2N	M.p. (°C)
34	Isopropyl	4-Chlorophenyl	Dibutylamino	165 (HCl)
35	Isopropyl	4-Chlorophenyl	Dipropylamino	176 (HCl)
36	Isopropyl	4-Chlorophenyl	Diallylamino	118
37	Isopropyl	4-Chlorophenyl	Di(2-methoxyethyl)amino	127 (HCl)
38	Isopropyl	4-Chlorophenyl	Perhydroazepin-1-yl	68
39	Isopropyl	4-Chlorophenyl	Benzylamino	108
40	Isopropyl	4-Chlorophenyl	(2-Methoxyethyl)amino	152 (HCl)
41	Isopropyl	4-Chlorophenyl	(2-Ethylmercaptoethyl)amino	148 (HCl)
42	Isopropyl	4-Chlorophenyl	(3-Morpholinopropyl)amino	245 (2HCl)
43	Isopropyl	4-Chlorophenyl	N-(Ethyl)-N-(benzyl)amino	Oil
44	Isopropyl	4-Chlorophenyl	4-Aminocarbonylpiperidino	189
45	Isopropyl	4-Chlorophenyl	1,3-Thiazolidin-3-yl	77
46	Isopropyl	4-Chlorophenyl	4-(Dimethylaminosulfonyl)-piperazino	150
47	Isopropyl	4-Chlorophenyl	4-Benzylpiperazino	265 (2HCl)
48	Isopropyl	4-Chlorophenyl	4-((Isopropylaminocarbonyl)-methyl)piperazino	133
49	tert-Butyl	4-Chlorophenyl	4-Methylpiperazino	122
50	tert-Butyl	4-Chlorophenyl	(2-Methoxyethyl)amino	94
51	tert-Butyl	4-Chlorophenyl	(3-Pyridylmethyl)amino	143
52	tert-Butyl	4-Chlorophenyl	Morpholino	136
53	tert-Butyl	4-Chlorophenyl	4-(Dimethylaminosulfonyl)-piperazino	168
54	tert-Butyl	4-Chlorophenyl	(2,2,6,6-Tetramethylpiperidin-4-yl)amino	142
55	Phenyl	4-Chlorophenyl	Morpholino	193
56	Phenyl	4-Chlorophenyl	4-Methylpiperazino	167
57	Phenyl	4-Chlorophenyl	(3-Pyridylmethyl)amino	130

Ex. No.	R^4	R^3	R^1R^2N	M.p. (°C)
58	Phenyl	4-Chlorophenyl	(3-(Imidazol-1-yl)propyl)amino	154
59	Phenyl	4-Chlorophenyl	(2-(3-Methoxyphenyl)ethyl)-amino	103 (HCl)
60	Phenyl	4-Chlorophenyl	4-Carboxy-1,3-thiazolidin-3-yl	113
61	Isopropyl	2-Thienyl	Pyrrolidino	74
62	Isopropyl	2-Thienyl	cis-2,6-Dimethylmorpholino	103
63	Phenyl	4-Chlorophenyl	Diethylamino	132
64	Phenyl	4-Chlorophenyl	Butylamino	95 (HCl)
65	Phenyl	4-Chlorophenyl	Thiomorpholino	175
66	tert-Butyl	4-Chlorophenyl	Thiomorpholino	119
67	Isopropyl	4-Pyridyl	Butylamino	101
68	Isopropyl	4-Pyridyl	(3-Phenylpropyl)amino	Resin
69	Phenyl	4-Chlorophenyl	Dipropylamino	72
70	Isopropyl	4-Chlorophenyl	Cyclopropylamino	Oil
71	CF_3	4-Chlorophenyl	(3-Pyridylmethyl)amino	181
72	Isopropyl	4-Chlorophenyl	3,3-Dimethylpiperidino	Oil
73	CF_3	4-Chlorophenyl	4-Methylpiperazino	108
74	CF_3	4-Chlorophenyl	Morpholino	184
75	tert-Butyl	4-Chlorophenyl	Perhydroazepin-1-yl	151
76	tert-Butyl	4-Chlorophenyl	4-Aminocarbonylpiperidino	164
77	Isopropyl	3,5-Dichlorophenyl	(trans-4-Hydroxycyclohexyl)-amino	174
78	Isopropyl	3,5-Dichlorophenyl	(2-Hydroxyethyl)amino	88
79	Isopropyl	3,5-Dichlorophenyl	Butylamino	190 (HCl)
80	Isopropyl	3,5-Dichlorophenyl	Diethylamino	Oil
81	Isopropyl	3,5-Dichlorophenyl	Morpholino	138
82	Isopropyl	3,5-Dichlorophenyl	Thiomorpholino	130
83	Isopropyl	3,5-Dichlorophenyl	4-Methylpiperazino	123
84	Isopropyl	3,5-Dichlorophenyl	Dipropylamino	Oil
85	Isopropyl	4-Methylphenyl	Dipropylamino	Oil
86	Isopropyl	4-Methylphenyl	Diethylamino	180 (HCl)
87	Isopropyl	4-Methylphenyl	(3-Hydroxypropyl)amino	86

Ex. No.	R^4	R^3	R^1R^2N	M.p. (°C)
88	Isopropyl	4-Methylphenyl	Butylamino	Oil
89	Isopropyl	4-Methylphenyl	Morpholino	95
90	Isopropyl	4-Methylphenyl	Thiomorpholino	107
91	Isopropyl	4-Methylphenyl	4-Methylpiperazino	70
92	Isopropyl	4-Chlorophenyl	N-(Ethyl)-N-(butyl)amino	Oil
93	Isopropyl	4-Chlorophenyl	N-(Methyl)-N-(butyl)amino	Oil
94	Isopropyl	4-Chlorophenyl	4-(2-Pyridyl)piperazino	166
95	CF_3	4-Chlorophenyl	4-(2-Pyridyl)piperazino	174
96	Isopropyl	4-Chlorophenyl	cis/trans-2,6-Dimethyl-morpholino	Oil
97	Isopropyl	4-Methylphenyl	cis-2,6-Dimethylmorpholino	Oil
98	Isopropyl	4-Methylphenyl	Di(2-methoxyethyl)amino	Oil
99	Isopropyl	4-Methylphenyl	4-Aminocarbonylpiperidino	192
100	Isopropyl	4-Methylphenyl	Perhydroazepin-1-yl	Oil
101	tert-Butyl	4-Chlorophenyl	cis-2,6-Dimethylmorpholino	117
102	tert-Butyl	4-Chlorophenyl	(3-Methoxypropyl)amino	Oil
103	tert-Butyl	4-Chlorophenyl	Di(2-methoxyethyl)amino	Oil
104	Isopropyl	4-Chlorophenyl	cis-2,6-Dimethylmorpholino	114
105	Isopropyl	4-Chlorophenyl	(2-Diisopropylaminoethyl)-amino	219 (2HCl)
106	Isopropyl	4-Chlorophenyl	4-(2-Hydroxyethyl)piperazino	227 (2HCl)
107	Isopropyl	4-Chlorophenyl	(1-Benzylpiperidin-4-yl)amino	250 (2HCl)
108	Phenyl	4-Chlorophenyl	cis/trans-2,6-Dimethyl-morpholino	187
109	Phenyl	4-Chlorophenyl	(3-Methoxypropyl)amino	Oil
110	Phenyl	4-Chlorophenyl	Di(2-methoxyethyl)amino	Oil
111	Phenyl	4-Chlorophenyl	4-Aminocarbonylpiperidino	204
112	Phenyl	4-Chlorophenyl	Perhydroazepin-1-yl	126
113	Isopropyl	4-Cyanophenyl	(4-Hydroxybutyl)amino	93
114	Isopropyl	4-Cyanophenyl	(3-Methoxypropyl)amino	70
115	Isopropyl	4-Cyanophenyl	Butylamino	89
116	Isopropyl	4-Cyanophenyl	Cyclopentylamino	141
117	Isopropyl	4-Cyanophenyl	(4-Hydroxycyclohexyl)amino	101

Ex. No.	R^4	R^3	R^1R^2N	M.p. (°C)
118	Isopropyl	4-Cyanophenyl	(3-Pyridylmethyl)amino	149
119	Isopropyl	4-Cyanophenyl	Dipropylamino	80
120	Isopropyl	4-Cyanophenyl	Perhydroazepin-1-yl	117
121	Isopropyl	4-Cyanophenyl	Morpholino	224
122	Isopropyl	4-Cyanophenyl	4-Methylpiperazino	152
123	Isopropyl	2-Methylthiazol-4-yl	Dipropylamino	Oil
124	Isopropyl	4-Chlorophenyl	Cyclopentylamino	82
125	Isopropyl	4-Chlorophenyl	(trans-4-Hydroxycyclohexyl)-amino	138
126	Isopropyl	4-Chlorophenyl	(trans-4-Aminocyclohexyl)-amino	128
127	Isopropyl	4-Chlorophenyl	(cis/trans-4-Hydroxycyclo-hexyl)amino	Oil
128	Isopropyl	4-Chlorophenyl	(4-Methylcyclohexyl)amino	Oil
129	Isopropyl	4-Chlorophenyl	N-(Cyclohexyl)-N-(methyl)amino	88
130	Isopropyl	4-Chlorophenyl	(2-Isopropyl-5-methylcyclohexyl)amino	Oil
131	Isopropyl	4-Chlorophenyl	(trans-2-Hydroxycyclohexyl)-amino	Oil
132	tert-Butyl	4-Chlorophenyl	Cyclopentylamino	89
133	tert-Butyl	4-Chlorophenyl	(trans-4-Hydroxycyclohexyl)-amino	173
134	CF_3	4-Chlorophenyl	Cyclopentylamino	99
135	Phenyl	4-Chlorophenyl	(trans-4-Hydroxycyclohexyl)-amino	95
136	Isopropyl	4-Chlorophenyl	4-Hydroxypiperidino	121
137	Isopropyl	4-Chlorophenyl	(4-Hydroxybutyl)amino	Oil
138	Isopropyl	4-Chlorophenyl	(Benzimidazol-2-ylmethyl)-amino	112
139	Isopropyl	4-Chlorophenyl	Cyclobutylamino	70
140	Isopropyl	4-Chlorophenyl	Cyclononylamino	Oil
141	Isopropyl	4-Chlorophenyl	3-Diethylaminocarbonyl-piperidino	Oil
142	Isopropyl	4-Chlorophenyl	((R)-1-Phenylethyl)amino	Oil

Ex. No.	R^4	R^3	R^1R^2N	M.p. (°C)
143	Isopropyl	4-Chlorophenyl	((S)-1-Phenylethyl)amino	Oil

Example 144

2-(4-Chlorophenyl)-6-isopropyl-4-(1-oxothiomorpholino)pyrimidine

0.25 g of 2-(4-chlorophenyl)-6-isopropyl-4-thiomorpholinopyrimidine was dissolved in 1 ml of glacial acetic acid and treated with 0.068 ml of a 35% strength hydrogen peroxide solution. After 2 hours, the mixture was diluted with 20 ml of water and the product was extracted with ethyl acetate. The ethyl acetate phase was extracted twice by shaking with 10 ml of water and the organic phase was concentrated after drying over sodium sulfate. The residue was recrystallized from isopropanol. Yield: 0.18 g.

M.p.: 171°C.

The following sulfoxides and sulfones were prepared analogously:

Example 145

2-(4-Chlorophenyl)-6-isopropyl-4-(1,1-dioxothiomorpholino)pyrimidine; m.p.: 226°C

Example 146

2-(4-Chlorophenyl)-6-isopropyl-4-(1-oxo-1,3-thiazolidin-1-yl)pyrimidine; m.p.: 128°C

Example 147

2-(4-Chlorophenyl)-4-((2-ethylsulfinylethyl)amino)-6-isopropylpyrimidine; m.p.: 103°C

Example 148

6-Isopropyl-2-(4-methylphenyl)-4-(1-oxothiomorpholino)pyrimidine; m.p.: 152°C

Example 149

2-(3,5-dichlorophenyl)-6-isopropyl-4-(1-oxothiomorpholino)pyrimidine; m.p.: 187°C

Pharmacological investigations

Activation of soluble guanylate cyclase

The activation of soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and pyrophosphate, by the compounds according to the invention was quantified with the aid of an enzyme immunoassay (EIA) from Amersham. For this, the test substances were first incubated with sGC in microtiter plates and then the quantity of the resulting cGMP was determined.

The sGC employed had been isolated from bovine lung (see Methods in Enzymology, Volume 195, p. 377). The test solutions (100 µl per well) contained 50 mM triethanolamine (TEA) buffer (pH 7.5), 3 mM $MgCl_2$, 3 mM reduced glutathione (GSH), 0.1 mM GTP, 1 mM 3-isobutyl-1-methylxanthine (IBMX), suitably diluted enzyme solution and the test substance or, in the control experiments, solvent. The test substances were dissolved in dimethyl sulfoxide (DMSO) and the solution was diluted with DMSO/water such that the final concentration c of test substance in the test batch was 50 µM. The DMSO concentration in the test batch was 5% (v/v). The reaction was started by addition of the sGC. The reaction mix was incubated at 37°C for 15 to 20 minutes and then stopped by ice-cooling and addition of the stop reagent (50 mM EDTA, pH 8.0). An aliquot of 50 µl was taken and employed for the determination of the cGMP content using the acetylation protocol of the Amersham cGMP EIA kit. The absorption of the samples was measured at 450 nm (reference wavelength 620 nm) in a microtiter plate reading apparatus. The cGMP concentration was determined by means of a calibration curve, which was obtained under the same experimental conditions. The activation of the sGC by a test substance is indicated as n-fold stimulation of the basal enzyme activity which was found in the control experiments (with solvent instead of test substance) (calculated according to the formula

n-fold stimulation = $[\text{cGMP}]_{\text{test substance}} / [\text{cGMP}]_{\text{control}}$).

The following results were obtained:

Compound of Example No.	n-fold stimulation at c = 50 µM
23	>8
25	28
29	>4
30	>4
32	>4
33	>16
34	>4
35	>16
36	>8
38	>8
43	>4
44	>4
45	>4
52	>8
63	>8
66	>4
69	>4
77	30
79	>4
80	>16
81	>4
82	>4
84	>16
85	>16
86	>16
88	>8
89	>8
90	>16
97	>16
98	>8
99	>4
100	>8
112	>8

Compound of Example No.	n-fold stimulation at c = 50 µM
124	>16
125	32
133	>16
137	>16